2018-07-29

A Chronology for the Identification and Disclosure of Adverse Effects of Succinylcholine

Lisa Huang
University of Massachusetts Medical School

Et al.

Accepted Manuscript

A Chronology for the Identification and Disclosure of Adverse Effects of Succinylcholine

Lisa Huang, Christine N. Sang, Manisha S. Desai

PII: S2352-4529(18)30094-X
DOI: doi:10.1016/j.janh.2018.07.003
Reference: JANH 208

To appear in: *Journal of Anesthesia History*

Received date: 4 July 2018
Accepted date: 25 July 2018

Please cite this article as: Lisa Huang, Christine N. Sang, Manisha S. Desai , A Chronology for the Identification and Disclosure of Adverse Effects of Succinylcholine. Janh (2018), doi:10.1016/j.janh.2018.07.003

A chronology for the identification and disclosure of adverse effects of succinylcholine

Lisa Huang, B.A.* †

Christine N. Sang, M.D. ‡

Manisha S. Desai, M.D. *§

*University of Massachusetts Medical School, Worcester, Massachusetts

†Medical Student

§Associate Professor of Anesthesiology

‡Associate Professor of Anaesthesia

Harvard Medical School – Brigham and Women's Hospital, Boston, Massachusetts

This study was supported by intramural funds.

Lisa Huang is a recipient of a Wood Library-Museum of Anesthesiology Fellowship Award

Corresponding Author: Lisa Huang, B.A.

Lisa.Huang@umassmed.edu

University of Massachusetts Medical School, Worcester, Massachusetts

55 Lake Avenue North, Worcester, Massachusetts 01655

Keywords: adverse effects, side effects, succinylcholine

Abstract

Background: New therapies are created to address specific problems and enjoy popularity as they enter widespread clinical use. Broader use can reveal unknown adverse effects and impact the life cycle significantly. Succinylcholine, a depolarizing neuromuscular blocker, was the product of decades of research surrounding the ancient compound, curare. It was introduced into practice in the 1940s by Burroughs Wellcome and Company (BW Co.) and was welcomed due to its rapidly acting muscle relaxation effects. Global clinical use revealed adverse effects, both minor and major, in particular, hyperkalemia and malignant hyperthermia. We investigated when practitioners and the manufacturer became aware of these adverse effects, how information about these side effects were disseminated, and whether the manufacturer met the regulatory requirements of the time, specifically regarding the timely reporting of adverse effects.

Sources: Primary literature search using online and archived documents was conducted at the Wood Library-Museum of Anesthesiology, Schaumburg, Illinois. We consulted documents submitted by BW Co. to federal authorities, through the Freedom of Information Act (FOIA), Food and Drug Administration (FDA) reports, promotional advertisements, package inserts, published articles, and textbooks.

Results: Initial clinical testing in humans in 1952 found no adverse effects on cardiovascular or respiratory systems. Fasciculations and myalgia were early side effects described in case reports in 1952. Large-scale clinical trials in 1953 found abnormally long recovery times among some patients; the discovery of abnormal pseudocholinesterase enzyme activity was not fully demonstrated until the early 1960s. Bradycardia was first reported in 1957 in children, and in 1959 in adults. In 1960, animal studies reported a transient increase in plasma potassium; further experiments in 1969 clearly demonstrated succinylcholine-induced hyperkalemia in burn

patients. Malignant hyperthermia was first described in 1966. Similar cases of elevated temperatures and muscle rigidity were described globally but the underlying mechanism was not elucidated until the 1990s. Standard anesthesia textbooks did not report major side effects of succinylcholine until 1960 and included newly documented side effects with each edition. BW Co.'s packaging contained warnings as early as the 1950's but were later updated in 1962 and beyond to reflect the newly discovered hyperkalemia and malignant hyperthermia.

Conclusion: Particularly given the regulatory environment of the time, BW Co. appropriately reported the adverse effects of succinylcholine after market entry; it updated promotional and packaging material in a timely manner to reflect newly discovered adverse effects. The toxicity, though alarming and put clinicians on alert, did not seem to heavily impact succinylcholine's use, given its various desirable properties. It is still a choice muscle relaxant used today, although there are efforts to develop superior agents to replace succinylcholine.

Introduction

Pharmacological and nonpharmacological treatments possess a life cycle like that of newly introduced products in our daily lives. The novelty of a new and different drug attracts early adopters who are eager to test out the promised effects, after which there is a general acceptance by clinicians at large. Often, with broader use and off-label use, the adverse effects of the drug appear, with some that are predicable while others are not. Over time, enthusiasm for these drugs may wane as the reality of harmful side effects sets in and as investigators discover replacements with improved safety and efficacy, just as these drugs may have replaced earlier ones. These drugs disappear from the scene permanently when they are no longer commercialized.

We discuss the introduction, evolution of use, identification and publicizing of side effects of a commonly used medication in modern anesthetic practice: succinylcholine, also known as suxamethonium chloride (international nonproprietary name). D-Tubocurarine had been introduced into clinical use in the 1930s and was extremely useful for surgical procedures involving the abdomen. However, its duration of action (30-60 minutes) was too long for short procedures such as electroconvulsive therapy, dental extraction, tracheal intubation, and operations of a short duration. Succinylcholine fulfilled the requirements for the aforementioned short procedures, and continuous infusions were used for longer procedures as well.

As the drug was being developed for clinical use, the manufacturer, Burroughs Wellcome and Company (BW Co.), would have conducted investigations to determine clinical efficacy while also noting adverse effects. We sought to determine if clinically significant adverse reactions may have been evident in retrospect and should have been included in the marketing materials.

The United States Food and Drug Administration (FDA)'s pharmaceutical approval process underwent numerous amendments over its existence. The 1938 Federal Food, Drug, and Cosmetic Act began requiring manufacturers to demonstrate product safety prior to approval for marketing. [1] Specific requirements by the FDA for the disclosure of risk information in advertising materials and promotional labeling were tied to the expansion of its authority. [2] In 1951, Congress passed the Durham Humprey Amendment, which required that specific drugs be prescribed by a medical professional. This was the first time that there was a statutory definition of drugs based on defined criteria. A period followed in which promotional materials were everywhere; interestingly, the FDA did not regulate advertising in medical journals; this was the role of the Federal Trade Commission (FTC; Wheeler Lea Act, 1938). In fact, claims of efficacy were often made despite a lack of evidence. In part because evidence for causality (particularly with low frequency adverse events) is best inferred from large systematic clinical trials that may not have been available at the time, safety was typically assumed. Thus, congressional hearings on pharmaceutical marketing practices ensued, accelerated by an observation in Europe that thalidomide was associated with serious birth defects.

The Federal Trade Commission (FTC) is also granted oversight of advertising for FDA-regulated materials. In the years leading up to the discovery of succinylcholine, the FDA developed more regulations, including guidelines of good manufacturing practices for quality control in 1941, banning illegal drug sales in 1948, clarification of use on drug labels in 1950, and the limitation of sale of drugs meant to be used by medical professionals in the 1951 Durham-Humphrey Amendment. [3] In 1952, a voluntary program to report drug reactions was formed and a decade later, the Kefauver-Harris Amendments were passed in 1962, which not only required manufacturers to prove product efficacy through controlled clinical trials prior to

approval, but also to report any serious side effects after market entry. [4] These amendments also transferred the control of pharmaceutical advertising to the FDA. In the years that followed, the FDA put forth further rules to regulate clinical trials, including the Investigational New Drug and New Drug Application approval pathways; these required manufacturers to demonstrate new agents' safety through different phases of testing, as well as approval from an Institutional Review Board of information pertaining to the sponsors, methods, and patients involved before the study was allowed to be conducted. [5] The Fair Packaging and Labeling Act of 1966 required all products to have honest and informative labels and the FDA required package inserts with information about risks and benefits for all medications starting in 1970.The development of enhanced safety standards through the 1970s by the FDA formed the backdrop for establishing a legal responsibility and accountability for BW Co. in its production and marketing of succinylcholine. We investigate marketing material and package inserts by BW Co. for succinylcholine over three decades to track the updates in listed side effects.

Sources

Primary literature search was conducted at the Wood Library-Museum of Anesthesiology, Schaumberg, Illinois, using archived documents and online databases. Archived documents consisted of advertisements in early editions of anesthesia journals, physical copies of original research articles, case reports, drug package inserts, drug information packets, and other manufacturer marketing materials. We also reviewed documents submitted to the Federal Drug Administration (FDA) by BW Co. for approval of succinylcholine's use in the clinical setting (through the Freedom of Information Act) and other FDA reports. We examined updated editions of anesthesia and pharmacology textbooks to ascertain when information about adverse effects

was published in standard medical textbooks, specifically Goodman and Gilman's *Pharmacological Basis of Therapeutics*, Dripps/Eckenhoff/Vandam's *Introduction to Anesthesia*, Collins' *Principles of Anesthesiology*, and Wylie's *A Practice of Anaesthesia*. We reviewed the textbooks' sections on neuromuscular blocking agents and adverse effects, specifically, hyperkalemia, and malignant hyperthermia.

History and Synthesis

The history of neuromuscular blocking agents can be traced back to curare. This plant extract was used by aboriginal tribes in South America to hunt wild animals for centuries. Its notable paralytic effect on the respiratory system of animals was carried into clinical practice in the 1800s, when curare was used to treat tetanus. In 1856 Claude Bernard conducted detailed laboratory experiments to elucidate the drug's mechanism and site of action. [6] Attempts were made to purify and then synthesize the compounds that gave curare its properties. This resulted in the isolation of d-tubocurarine by Harold King in 1935. King's discovery prompted further pharmacological investigation into compounds that mimicked the structure of d-tubocurarine, especially its two separated quaternary groups, which were thought to be responsible for the neuromuscular block. [7]

Three different groups reported the action of succinylcholine at the neuromuscular junction from 1949-1950: one led by Nobel-prize winner Daniel Bovet in Italy, one led by James Walker in the U.K., and one led by Edwin de Beer in the U.S. [8-11] It should be noted that Reid Hunt originally developed succinylcholine in 1906 through his studies of acetylcholine but conducted his experiments of succinylcholine in the presence of curare, and thus succinylcholine's muscle relaxation properties went unnoticed. [12]

De Beer and Castillo's report on succinylcholine in the 1950s described its neuromuscular blocking action in animal studies. [8] The compound was tested on cats, dogs, rabbits, mice, and frogs. The authors noted that the paralysis produced was on par with d-tubocurarine's effects, even with a very low dose succinylcholine, and marveled at its rapid onset and duration of the neuromuscular block. They did not observe any effects on blood pressure. They remarked that the action of succinylcholine could be prolonged by the administration of anticholinesterase inhibitors (such as physostigmine), whereas the action of d-tubocurarine was antagonized and nearly abolished by anticholinesterase inhibitors. These findings were consistent with previous observations by Bovet-Nitti. [8] At the time, Castillo's and Bovet-Nitti's teams assumed that the prolongation of action was due to physostigmine antagonizing a downstream enzyme that metabolized succinylcholine. Bovet's animal studies in 1951 found that large doses of succinylcholine caused transient hypertension. [13]

Succinylcholine was manufactured as an iodized salt, and also as succinylcholine chloride. [14, 15] The iodized salt was water soluble, but would undergo spontaneous breakdown over time, requiring clinicians to either dissolve it immediately prior to use or administer it subsequently without knowing how much active ingredient remained. [16] Moreover, patients allergic to iodinated products and shellfish could receive the chlorinated compound safely. [17] As a result, succinylcholine chloride is the form in which the drug has been manufactured ever since.

Adverse Effects Publicized

In 1952, Thesleff's group in Stockholm reported that an injection of succinylcholine caused fasciculations initially, and these were followed by muscle paralysis in animals.

Fasciculations were fairly common side effect that was reported in nearly every study that described the use of succinylcholine. [14, 18, 19]

Thesleff's group also reported that doses greater than 2mg/kg caused transient increases in blood pressure in animals. Doses greater than 30mg/kg caused bradycardia or cardiac arrhythmias in animals. [14] Bradycardia wasn't reported in human subjects until 1957, where it was first described in young children and infants. [20] In 1959, Bullough, commenting on a manuscript published in the previous year by Martin, summarized their findings on adult patients: bradycardia occurred following repeated administrations of succinylcholine, sometimes with leading to arrhythmias or cardiac arrest, recommending premedication with atropine if repeated dosing was required. [21]

Initial clinical testing on over 1,000 patients reported no effects on blood pressure, pulse, or salivation, no bronchospasm, and no histamine liberation. [15, 22, 23] An early description of the safety and efficacy of succinylcholine was reported with self-administration in 1952. The author suggested that the drug was safe and could be used to provide muscle relaxation during abdominal and thoracic operations, facilitate tracheal intubation, overcome laryngospasm, and be used as an adjunct during electroconvulsive therapy. [24] Other case reports in 1952 began to draw attention to abnormally long recovery times in some patients, which contradicted succinylcholine's characteristic short duration of action. [25, 26] This alarming adverse effect of prolonged apnea was confirmed in large-scale clinical trials in 1953. The explanation proposed at the time was that these patients had lower cholinesterase levels, meaning they were unable to metabolize succinylcholine at a normal rate. [27-29] The reasoning evolved as it became clear that the true problem lay within cholinesterase enzyme activity and abnormalities, and not levels.

However, in certain clinical states such as pregnancy and liver disease, low levels of normal enzyme too could result in a prolonged block from succinylcholine.

Myalgia in patients following the administration of another neuromuscular blocker, decamethonium, prompted investigations into the possibility of myalgia following succinylcholine use in patients. This side effect was briefly mentioned in Bourne's 1952 publication, where it was stated that patients who experienced vigorous fasciculations were more likely to experience postoperative muscle stiffness. [25] In 1954, Churchill-Davidson conducted a trial comparing the rates of muscle pain between patients who received succinylcholine for outpatient procedures versus inpatient procedures (i.e. confined to the hospital for at least 48 hours postoperatively). [30] For the outpatient group, 66% of patients reported generalized myalgias and stiffness starting postoperative day one. Only 14% of patients in the inpatient procedures group reported myalgia one day after their procedures. Churchill-Davidson attributed the difference in the rate of myalgia to the fact that the inpatient group was confined to bedrest after succinylcholine use. This report initially didn't receive much attention but studies followed in 1956 and 1957 that reported incidences of postoperative muscle pains from 20 to 70% associated with succinylcholine. [31, 32] Numerous trials were conducted through the next decades to determine what pharmaceutical agents can help prevent the development of myalgia, a side effect that ranged from being a mild nuisance to temporarily debilitating for some patients. A meta-analysis of 52 studies by Schreiber et al in 2005 concluded that nonsteroidal anti-inflammatory drugs (NSAIDs), rocuronium, and lidocaine were most effective at preventing myalgia. [33] The meta-analysis also could not establish a correlation between the incidence of fasciculations and myalgia, suggesting that they are caused by different mechanisms, and thus an agent that prevents fasciculations may not necessarily prevent myalgia.

Animal studies conducted in 1960 showed that administration of succinylcholine produced a transient increase in plasma potassium, which might have been one of the earliest warnings of hyperkalemia caused by succinylcholine. [34] Though earlier studies identified the contraindication of succinylcholine in burn patients, which usually resulted in cardiac arrest, the mechanism underlying this side effect was undetermined. [35, 36] In 1969, Schaner and colleagues performed a series of studies showing that the injection of succinylcholine in burn patients, between 20-60 days post-burn, produced hyperkalemia; hyperkalemia increases with larger burns and larger doses of succinylcholine and the authors cautioned its use in burn patients. [37] In 1973, animal studies demonstrated that denervated muscle, found in burn and trauma victims, underwent massive depolarization in response to succinylcholine, which increases membrane permeability to potassium, thus contributing to hyperkalemia. [38]

Another side effect associated with succinylcholine, malignant hyperthermia, began to appear in the literature in the late 1960s. In 1966, cases of malignant hyperthermia were described in Canada and a warning sign for this side effect was the unexplained muscle rigidity that followed succinylcholine administration, especially when combined with halothane. [39, 40] More reports followed from Britain, describing similar problems with elevated temperature following anesthesia but maintained that the cause was not entirely due to succinylcholine. [41] Numerous trials began, aiming to find the etiology of malignant hyperthermia. Denborough and colleagues determined that muscle rigidity was due to an increase in free intracellular calcium ions, precipitated by an anesthetic agent, and this resulted in persistent muscle contracture with a concomitant increase in energy utilization and excess heat production. [42] A breakthrough animal study in 1991 revealed that malignant hyperthermia was correlated with a mutation in the skeletal muscle ryanodine receptor (RyR1). [43]

Minor side effects such as fasciculations and myalgia were reported in the early editions of anesthesia textbooks. [44-46] The earliest major side effect reported was prolonged apnea; this appeared in textbooks by 1955, three years after initial case reports. [44, 46, 47] Bradycardia was mentioned in textbooks starting in 1960, hyperkalemia was discussed starting in 1965, and malignant hyperthermia appeared starting in 1970; all lagging a few years behind the original case reports since textbooks were only updated every few years. [46, 48-52] Other minor side effects were included as textbooks continued to update into the 1970s; these included increased intraocular pressure, a small amount of histamine release, a weal and flare production similar to that produced by d-tubocurarine administration, tachycardia and other cardiac irregularities, hypertension, and cardiovascular collapse.

Succinylcholine was marketed as "Anectine" by BW Co. Its booklets included precautions, contraindications, and warnings as early as 1952-1956 (estimated) about prolonged apnea due to plasma-cholinesterase activity, muscle stimulation, and increased intraocular pressure that cautions use in intraocular surgery. (Figures 1-3) BW Co.'s 1952 Anectine booklet's "Contraindications and Precautions" section warns against fasciculations and prolonged apnea. (Figure 1) Another Anectine booklet from 1954 includes a "Side Effects" section, which describes fasciculations as the only significant side effect. (Figure 2) A double-sided booklet insert from 1955 describes fasciculations as a side effect but otherwise notes that succinylcholine has "no toxic side effects", though it is unclear if the lack of side effects included on this advertisement is due to text constraints or a deliberate marketing decision. Single-paged advertisements in journals such as *Anesthesiology* and *Anesthesia & Analgesia* boasted succinylcholine's rapid acting properties but did not list side effects. (Figures 4-5) BW Co.'s own updated booklet in 1962 emphasized that succinylcholine had "virtually no toxicity;

virtually no side effects" in the beginning of the packet before listing prolonged apnea, fasciculations, and increased intraocular pressure under its "Contraindications and Precautions" section. (Figure 6) These warnings of adverse effects remained in other promotional material and only increased in number and detail. BW Co.'s 1975 booklet about Anectine included warnings about bradycardia, myalgia, malignant hyperthermia and hyperkalemia. (Figure 7) These side effects were not listed in the 1965 versions of the promotional material. Table 1 lists the appearance of complications in journals, textbooks in anesthesiology, and drug package inserts.

Documents submitted to the FDA from 1971 to 1973 by BW Co. provided some details pertaining to sterility and potency problems of the original packaging and reflected new information about toxicity. (Figure 8) The company also delayed sending current manufacturing information, prompting several reminders from the FDA. The application was initially marked incomplete since BW Co. did not include full reports of adequate Limulus Amebocyte Lysate testing, an endotoxin test required of all pharmaceuticals and devices that come in contact with blood of cerebrospinal fluid. The package insert updates were approved in December 1975, which included warnings of malignant hyperthermia and hyperkalemia in burn patients. (Figure 9) Other FDA documents noted that the resubmission of these applications "has been lengthy" and mostly due to insufficient data provided by the manufacturer. These documents point out that the company had been marketing succinylcholine (Flo-Pack) without an approved supplement for sterilization, and there was no specific mention about the suppression of known side effects. In 1981, during another package insert revision, the FDA made amendments to several sections, including the expansion of succinylcholine's list of contraindications and required an entire section devoted to malignant hyperthermia. These warnings remained on the package inserts, which continue to be revised and resubmitted as late as 2010.

Discussion

D-tubocurarine enjoyed a short period of popularity before case reports suggested several side effects related to histamine release – hypotension, bradycardia, bronchospasm, and increased salivary secretions. Updated textbook editions reflected these details, but advertisements and promotional materials were slow to include these side effects. It is unclear whether this was due to limitations in the size of the advertisement, or if the manufacturers did not include negative effects.

Efforts to replace d-tubocurarine may have resulted in the development of succinylcholine. Scientists set out to synthesize a new anesthetic that mimicked the structure of d-tubocurarine. One of these compounds was decamethonium and it was theorized that its success was due to a 10-atom distance between its two nitrogen atoms. Succinylcholine, once called diacetycholine, was synthesized with the same goal of a 10-atom distance between its nitrogen atoms, and its structure resembled two acetylcholine molecules laid end to end, giving it depolarizing neuromuscular blocking properties. Succinylcholine became a very popular choice of muscle relaxant due to its rapid onset and short duration as a result of its rapid breakdown in the body. It replaced d-tubocurarine as the relaxant of choice for tracheal intubation and short surgical procedures. D-tubocurarine continued to be used for longer operations.

The regulations surrounding drug development and marketing evolved during the same time succinylcholine was synthesized and manufactured. Succinylcholine was manufactured and marketed with a clear purpose on its labels, and with instruction to be used by medical professionals only. In compliance with the voluntary program to report drug reactions, researchers documented any side effect they thought were attributed to succinylcholine use in

their case reports. Following the Kefauver-Harris Amendments of 1962, reports continued to be published of new side effects despite succinylcholine's widespread market penetration by then. We found that BW Co. updated their packaging and marketing material to reflect new side effects and warnings, in line with the Fair Packaging and Labeling Act of 1966 and we found evidence the form of FDA documents of BW Co. updating their drug package inserts in 1970. Though it appears that BW Co. was slow at providing the required documents to the FDA and delayed the application, the manufacturer was compliant in updating its marketing and packaging material with new side effects in an appropriate manner.

Despite its shortcomings and well-documented side effects in promotional materials and package inserts, succinylcholine survives to this day in the U.S., unlike halothane and d-tubocurarine. Anesthesiologists still prefer its quick onset and short duration properties. Not surprisingly, this has prompted a search for new compounds that have the same action as succinylcholine without the side effects. Although newer agents may possess the ability to provide muscle relaxation quite rapidly, they suffer from prolonged duration of blockade. A recent development has been the introduction of a reversal agent sugammadex. This drug binds to steroid neuromuscular blockers such as rocuronium and vecuronium and inactivates them rapidly. Thus, in a roundabout manner, two agents administered in series can deliver the advantages offered by succinylcholine. A clinical trial compared the recovery time of rocuronium and sugammadex (to reverse the neuromuscular block) to succinylcholine; and found that of the rocuronium/sugammadex combination was shorter. [53, 54] However, sugammadex too is associated with side effects, including rare anaphylactic reactions. [55] Thus, it remains to be seen if this combination will successfully replace this long-standing muscle relaxant. We can look forward to newer relaxants to replace succinylcholine.

Conclusions

Anesthetic medications are bound to the same lifecycle as any other medication or consumer product. Their introduction, built upon years and decades of investigative efforts, fulfilled a specific niche in anesthesia and the relatively unregulated medical market allowed easy dissemination of the product to clinicians and researchers. These medications enjoyed great popularity during their early years as clinicians were eager to try drugs with novel properties. With broader use, some effects of the drugs that were previously undetected appeared. Initial single reports are often insufficient to influence the majority opinion but as more cases are reported, particularly when those with lethal outcomes capture the spotlight, further investigations, updated with the constantly growing knowledge of the medical field, are warranted to look for toxicity. Often, researchers choose to abandon the drug at this stage and look for better alternatives, but succinylcholine had too many clinical advantages to abandon it. The manufacturer amended the package insert and advertisements to warn against contraindications and adverse effects. Textbooks and other authoritative sources on pharmaceuticals also updated each edition to reflect additional side effects. Typically, by this time, clinicians become wary of the undesired outcomes of even those drugs with unique properties and moved on to other options. So, new clinical guidelines for succinylcholine were issued. Replacement drugs were and are continuing to be developed; the next few decades could present a new clinically relevant depolarizing muscle relaxant.

It’s difficult to say whether or not there will one day be a drug that will stay in use forever. The lifecycle of a medication seems to indicate that we will discover and confirm the adverse effects of drugs once they have widespread use and then move on to a better alternative.

As long as there is a need to improve pharmacological agents, there will be a drive for new discoveries.

EndNote Generated References

[1] The 1938 Food, Drug, and Cosmetic Act. In: Administration USFaD, editor.1938.

[2] Donohue J. A history of drug advertising: The evolving roles of consumers and consumer protection. Milbank Q. 2006;84:659-99.

[3] A History of the FDA and Drug Regulation in the United States. U.S. Food and Drug Administration; 2006.

[4] Kefauver-Harris Amendments. U.S. Food and Drug Administration; 1962.

[5] Junod SW. FDA and Clinical Drug Trials: A Short History. FDA.gov: U.S. Food and Drug Administration; 2008.

[6] Claude B. Analyse physiologique des propriétés des systèmes musculaire et nerveux au moyen de curare. Comptes Rendus Hebdomadaires Des Seances De l'Academie Des Sciences 1856;43:825-9.

[7] King H. 330. Curare alkaloids. Part I. Tubocurarine. Journal of the Chemical Society (Resumed). 1935:1381-9.

[8] Castillo JC, de Beer EJ. The neuromuscular blocking action of succinylcholine (diacetylcholine). J Pharmacol Exp Ther. 1950;99:458-64.

[9] Walker J. Some new curarising agents. Journal of the Chemical Society. 1950:193-7.

[10] Bovet D, Bovet-Nitti F, Guarino S, Longo VG, Marotta M. Proprietá farmacodinamiche di alcuni derivati della succinilcolina dotati di azione curarica. Esteri di trialchiletanolammonio di acidi bicarbossilici alifatici. Rendic Ist Super Sanita. 1949;12:106-37.

[11] Berra L, Alston TA. Daniel Bovet: 1957 Nobel Laureate and Developer of Succinylcholine. Journal of Anesthesia History. 2015;1:76-8.

[12] Hunt R, Taveau RDM. On The Physiological Action Of Certain Cholin Derivatives And New Methods For Detecting Cholin The British Medical Journal. 1906;2:1788-91.

[13] Bovet D. Some aspects of the relationship between chemical constitution and curare-like activity. Ann N Y Acad Sci. 1951;54:407-37.

[14] Thesleff S. The pharmacological properties of succinylcholine iodide; with particular reference to its clinical use as a muscular relaxant. Acta Physiol Scand. 1952;26:103-29.

[15] Thesleff S, Dardel OV, Holmberg G. Succinylcholine iodide; a new muscular relaxant. Br J Anaesth. 1952;24:238-44.

[16] O'Neil M. Succinylcholine iodide. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry; 2013.

[17] Jonecko A. [An allergic incident after use of succinylcholine iodide (celocurin)]. Zentralbl Chir. 1960;85:439-45.

[18] Butt NS. A report on the use of succinylcholine chloride in a thoracic unit. Br J Anaesth. 1952;24:245-51.

[19] Foldes FF, McNall PG, Borrego-Hinojosa JM. Succinylcholine: a new approach to muscular relaxation in anesthesiology. N Engl J Med. 1952;247:596-600.

[20] Leigh MD, Mc CD, Belton MK, Lewis GB, Jr. Bradycardia following intravenous administration of succinylcholine chloride to infants and children. Anesthesiology. 1957;18:698-702.

[21] J. B. Intermittent suxamethonium injections. Br Med J. 1959;1:786-7.

[22] Adamson DC, Kinsam FM. Succinyl choline chloride in anaesthesia; preliminary report. Anaesthesia. 1952;7:166-8.

[23] Mesham PR, Barton JD. A report on succinylcholine chloride (scoline), an ultra-short-acting muscle relaxant. S Afr Med J. 1952;26:727-8.

[24] Mayrhofer OK. Self-experiments with succinylcholine chloride; a new ultra-short-acting muscle relaxant. Br Med J. 1952;1:1332-4.

[25] Bourne JG, Collier HO, Somers GF. Succinylcholine (succinoylcholine), muscle-relaxant of short action. Lancet. 1952;1:1225-9.

[26] Evans FT, Gray PW, Lehmann H, Silk E. Sensitivity to succinylcholine in relation to serum-cholinesterase. Lancet. 1952;1:1229-30.

[27] Bourne JG. Long action of suxamethonium (succinylcholine) chloride. Br J Anaesth. 1953;25:116-29.

[28] Evans FT, Gray PW, Lehmann H, Silk E. Effect of pseudo-cholinesterase level on action of succinylcholine in man. Br Med J. 1953;1:136-8.

[29] Forbat A, Lehmann H, Silk E. Prolonged apnoea following injection of succinyldicholine. Lancet. 1953;265:1067-8.

[30] Churchill-Davidson HC. Suxamethonium (succinylcholine) chloride and muscle pains. Br Med J. 1954;1:74-5.

[31] Dunn CH, Morris DD. Suxamethonium chloride and postoperative muscle pain. Br Med J. 1957;1:383-4.

[32] Hegarty P. Postoperative muscle pains. Br J Anaesth. 1956;28:209-12.

[33] Schreiber JU, Lysakowski C, Fuchs-Buder T, Tramer MR. Prevention of succinylcholine-induced fasciculation and myalgia: a meta-analysis of randomized trials. Anesthesiology. 2005;103:877-84.

[34] Stevenson D. Changes in the blood electrolytes of anaesthetized dogs caused by suxamethonium. British Journal of Anaesthesia. 1960;32:364-71.

[35] Bush GH, Graham HA, Littlewood AH, Scott LB. Danger of suxamethonium and endotracheal intubation in anaesthesia for burns. Br Med J. 1962;2:1081-5.

[36] McCaughey TJ. Burn Mortality and the Anaesthetist. Can Anaesth Soc J. 1963;10:501-7.

[37] Schaner PJ, Brown RL, Kirksey TD, Gunther RC, Ritchey CR, Gronert GA. Succinylcholine-induced hyperkalemia in burned patients. 1. Anesth Analg. 1969;48:764-70.

[38] Gronert GA, Lambert EH, Theye RA. The response of denervated skeletal muscle to succinylcholine. Anesthesiology. 1973;39:13-22.

[39] [Malignant hyperpyrexia during general anaesthesia]. Can Anaesth Soc J. 1966;13:514-8.

[40] Thut WH, Davenport HT. Hyperpyrexia associated with succinylcholine-induced muscle rigidity: a case report. Can Anaesth Soc J. 1966;13:425-8.

[41] Murray BR, Williams PA. Malignant hyperpyrexia during anaesthesia for colectomy. Br Med J. 1969;1:488.

[42] Denborough MA. The pathopharmacology of malignant hyperpyrexia. Pharmacol Ther. 1980;9:357-65.

[43] Fujii J, Otsu K, Zorzato F, de Leon S, Khanna VK, Weiler JE, et al. Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. Science. 1991;253:448-51.

[44] Goodman LS, Gilman AG. The Pharmacological Basis of Therapeutics. 2nd ed. New York: The Macmillan Company; 1955.

[45] RD D, JE E, LD V. Introduction to Anesthesia. 2nd ed. Philadelphia: WB Saunders Company; 1961.

[46] Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960.

[47] RD D, JE E, LD V. Introduction to Anesthesia. 1st ed. Philadelphia: WB Saunders Company; 1957.

[48] Collins VJ. Principles of Anesthesiology. Philedelphia: Lea & Febiger; 1966.

[49] Collins VJ. Principles of Anesthesiology. 2nd ed. Philedelphia: Lea & Febiger; 1976.

[50] Goodman LS, Gilman AG. The Pharmacological Basis of Therapeutics. 3rd ed. New York: The Macmillan Company; 1965.

[51] Goodman LS, Gilman AG. The Pharmacological Basis of Therapeutics. 4th ed. New York: The Macmillan Company; 1970.

[52] RD D, JE E, LD V. Introduction to Anesthesia. 3rd ed. Philadelphia: WB Saunders Company; 1967.

[53] Girard T. Pro: rocuronium should replace succinylcholine for rapid sequence induction. Eur J Anaesthesiol. 2013;30:585-9.

[54] Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. Anesthesiology. 2009;110:1020-5.

[55] Ikeda-Miyagawa Y, Kihara T, Matsuda R. [Case of negative pressure pulmonary edema after administration of sugammadex under general anesthesia with laryngeal mask airway]. Masui. 2014;63:1362-5.

Figure 1. BWC Anectine booklet, 1952 (estimated), pages 1 and 3

'ANECTINE'

CHLORIDE BRAND

SUCCINYLCHOLINE CHLORIDE

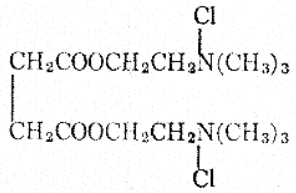
STERILE SOLUTION

CAUTION: Succinylcholine Chloride may produce respiratory depression as a result of general muscular paralysis. While respiratory depression is usually of very short duration following a single dose of the drug, or following cessation of continuous intravenous administration, there may on occasion be more prolonged respiratory depression requiring controlled respiration and the administration of oxygen. The drug should be used only by those skilled in the administration of controlled respiration and facilities for this procedure and for the administration of oxygen should always be immediately available. Neostigmine and other anticholinesterases, as well as Tensilon, do not antagonize the action of Succinylcholine, but on the contrary prolong its effect. They are therefore contraindicated as antidotes for Succinylcholine.

'ANECTINE' Chloride brand Succinylcholine Chloride is an ultra-short-acting skeletal muscle relaxant, that is, following intravenous injection of small doses (10 mg. to 20 mg.) the relaxation persists approximately three minutes. For prolonged relaxation 'ANECTINE' may be given by continuous intravenous drip. The degree of relaxation may be controlled by adjusting the rate of flow of the solution. Upon stopping the intravenous drip, spontaneous respiration ordinarily resumes within a minute and recovery is complete within 5 minutes. The quick return of spontaneous respiration is a definite advantage. Tachyphylaxis does not occur and cumulative action is not ordinarily seen.

CHEMICAL PROPERTIES

Succinylcholine chloride, also referred to as diacetylcholine chloride, is a white, odorless, crystalline substance which is readily soluble in water. Chemically it is succinic acid bis (β-dimethyl-aminoethyl) ester dimethochloride, and its formula is as follows:



The ester linkage is rapidly hydrolyzed in alkaline solutions but is relatively stable in acid solutions. In order to promote stability, solutions should be kept under refrigeration. It appears that succinylcholine is rapidly hydrolyzed following its injection and that this accounts for its extremely short duration of action and the rapid recovery of normal muscle tone.

PHARMACOLOGICAL ACTION

'ANECTINE' causes muscular paralysis by producing a blockage of nervous transmission at the myoneural junction. This action was first reported by Bovet et al.[1] Independent studies at The Wellcome Research Laboratories have been conducted on the synthesis[2] and pharmacology[3-7] of the drug. de Beer and his associates [3-7] have found that doses as low as 0.05 mg./Kg. given intravenously to cats are effective in producing muscular relaxation, and that intravenous doses of 0.1 mg./Kg. or more produce prompt and complete muscular paralysis which is characterized by short duration of action and extremely rapid recovery. Repeated injections produce reproducible and predictable muscular paralysis, neither tachyphylaxis nor significant cumulative effects being seen. 'ANECTINE' exerts its action independently of the presence of either 'Syncurine' brand Decamethonium Bromide or d-tubocurarine, but if given while either of these drugs is exerting its muscle relaxant effect, it would produce an added degree of muscular relaxation.

For the Medical Profession only

Short Procedures: The short duration of action of 'Anectine' Chloride (usually about 3 minutes following a single intravenous injection) makes it ideally suited for procedures requiring only brief relaxation such as endotracheal intubation, endoscopic examinations, orthopedic manipulations, short surgical procedures such as tonsillectomies, and electroshock therapy. The optimum intravenous dose for such purposes will vary among individuals, usually ranging from 10 to 30 mg. For this purpose an intravenous technique may be used, but generally it will be more convenient to administer a single intravenous injection. For the latter procedure the 10 cc. *multiple-dose vial* of 'Anectine' Chloride Injection containing *20 mg. per cc.* should be used (see listing at end of circular).

NOTE: Succinylcholine is rapidly hydrolyzed by alkaline solutions and therefore loses potency rapidly if mixed with thiopental sodium (pentothal sodium). Such mixtures, if used at all, must be used immediately; however, separate injection of 'ANECTINE' is preferable. In order to promote stability 'ANECTINE' should be kept under refrigeration.

CONTRAINDICATIONS AND PRECAUTIONS

The drug should be used only by those skilled in the administration of controlled respiration and facilities for this procedure and for the administration of oxygen should always be immediately available.

'ANECTINE' is not an anesthetic agent and should not be regarded as a substitute for anesthesia.

Some anesthesiologists believe that rapid injection is responsible for the muscular twitching that is seen just prior to relaxation. These fasciculations may be due to the rate of injection of the drug, and may be minimized or avoided by giving the injection more slowly.[8,23]

While respiratory depression is usually of very short duration following a single dose of the drug, or following cessation of continuous intravenous administration, there may be on occasion, especially with excessive doses, more prolonged respiratory depression[19,21] requiring controlled respiration and the administration of oxygen.

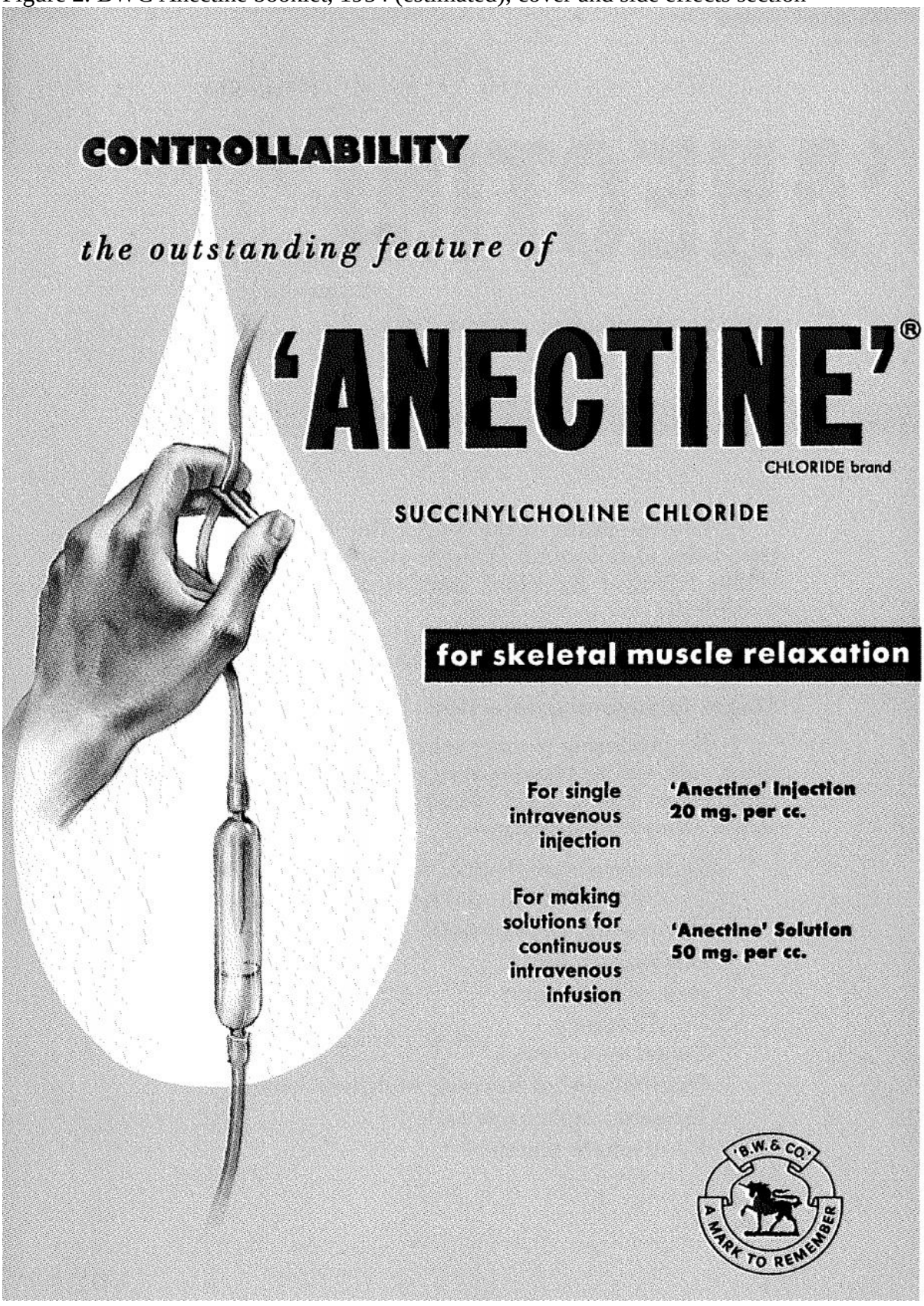
The duration of the effect of 'ANECTINE' may depend on plasma-cholinesterase activity.[24,26,27] Patients with severe liver disease, severe anemia, severe malnutrition, and possibly those suffering from polyphosphate insecticide poisoning may have a decreased plasma-cholinesterase activity which may intensify and prolong the action of 'ANECTINE', especially if large doses are used.[28,29] In such cases, in addition to the usual measures of controlled respiration and administration of oxygen, it may be desirable to administer plasma or whole blood for the purpose of restoring cholinesterase activity.[28]

Neostigmine and other anticholinesterases, as well as Tensilon, do not antagonize the action of 'ANECTINE', but on the contrary prolong its effect. They are therefore contraindicated as antidotes for 'ANECTINE'. Intravenous injections of procaine likewise may prolong and intensify the action of 'ANECTINE'.

BIBLIOGRAPHY

1. Bovet, D., Bovet-Nitti, F., Guarino, S., Longo, V. G., and Marotta, M.: Pharmacodynamical property of certain derivatives of succinylcholine with curare-like action—esters of trialkylethanolamine of dicarboxylic aliphatic acids. Rendiconti Istituto Superiore di Sanita 12:106, 1949.
2. Phillips, A. P.: Synthetic curare substitutes from aliphatic dicarboxylic acid aminoethyl esters. J. Am. Chem. Soc. 71:3264, 1949.
3. Castillo, J. C. and de Beer, E. J.: Potentiation of curarizing action of diacetylcholine (succinylcholine) by aliphatic dicarboxylic acid aminoethyl amides. Federation Proceedings 9:262, 1950.
4. Castillo, J. C. and de Beer, E. J.: The neuromuscular blocking action of succinylcholine (diacetylcholine). J. Pharmacol. & Exper. Therap. 99:458, 1950.
5. de Beer, E. J., Castillo, J. C., Phillips, A. P., Fanelli, R. V., Wnuck, A. L., and Norton, S.: Synthetic drugs influencing neuromuscular activity. Ann. New York Acad. Sci. 54:262, 1951.
6. Wnuck, A. L., Norton, S., Ellis, C. H., and de Beer, E. J.: Production of controlled neuromuscular block by infusion of diacetylcholine. Federation Proceedings 11:403, 1952.
7. Ellis, C. H., Norton, S., and Morgan, W. V.: Central depression by drugs which block neuromuscular transmission. Federation Proceedings 11:42, 1952.
8. Foldes, F. F., and McNall, P. G.: Succinylcholine: A new approach to muscular relaxation in anesthesiology. The New England J. of Med. 247:596, (Oct. 16) 1952.
9. Brucke, H., Ginzel, K. H., Klupp, H., Pfaffenschlager, F., and Werner, G.: Muscle relaxing effects of bis-choline ester of dicarboxylic acid in narcosis. Wien. Klin. Wschr. 63:464, 1951.
10. Ginzel, K. H., Klupp, H., and Werner, G.: Pharmacology of α, ω-bis-quarternary ammonium compounds. Comparative tests with some aliphatic dicarboxylic acid esters. Arch. int. Pharmacodyn. and Therapy 87:79, 1951.
11. Ginzel, K. H., Klupp, H., and Werner, G.: A dicholine ester with greater curare effect. Experentia 7:72, 1951.

Figure 2. BWC Anectine booklet, 1954 (estimated), cover and side effects section



SIDE EFFECTS

'Anectine' is remarkably free from side effects even when given in doses several times larger than those used clinically. Even large doses have no direct effect on the heart or central nervous system. Clinical doses do not affect transmission in the autonomic nervous system. The drug does not interfere with metabolism or liver function, for the products of its hydrolysis, namely, succinic acid and choline, are both naturally occurring metabolites.[1, 4, 15]

The only significant side effect of 'Anectine' is the transient initial muscle stimulation which precedes the relaxation. This action is most apparent when the injection is given rapidly; it is manifested as diffuse uncoordinated fasciculations of muscle bundles or groups. Twitchings may be observed 15 to 60 seconds after beginning the injection; they may last from 10 to 120 seconds; their disappearance marks the onset of relaxation. These preliminary fasciculations are usually infrequent and of negligible intensity if the injection is given slowly—a point to be remembered when 'Anectine' is to be given for manipulation of fractures and dislocations.

Figure 3. BWC Anectine booklet 1955 (estimated)

For the Medical Profession only

'ANECTINE'® Chloride brand

Succinylcholine Chloride

Ultra-short-acting skeletal muscle relaxant

CONTROLLABILITY is the outstanding feature of 'Anectine'-induced relaxation. It is the result of rapid onset of action, followed by rapid inactivation of the drug by hydrolysis.

Rapid onset of action	Relaxation obtained in half to one minute. (Fasciculations may appear about 15 seconds after injection; they may last 10 to 60 seconds; their disappearance marks the onset of relaxation.)
Brief duration of action	Relaxation, from a single injection, lasts about 2 minutes.
Rapid recovery	Complete return of muscle tone within a few minutes of injection. Muscle tone begins to recover immediately on stopping infusion.
Constant effect	Repeated administration of identical single doses will produce identical effects in the same patient, provided enough time for hydrolysis (usually 3 to 5 minutes) is allowed between each.
Absence of tachyphylaxis	When given continuously the effect of 'Anectine' remains constant without evidence of accumulation or tolerance.
Dose/response relationship	The critical dose for infusion lies at approximately 50 mcg. per Kg. per minute (3.5 mg./minute for a 70 Kg. patient). This dose will produce adequate muscular relaxation, but at the same time considerable respiratory depression. Assisted or controlled respiration is recommended, therefore, at this dose level.
Apnea	Cessation of respiration may occur at the peak of action of a single dose; spontaneous respiration usually returns within a few seconds to 4 minutes.
Placental barrier	Some clinical results suggest that maternally injected 'Anectine' does not reach the baby. Others report that though, occasionally, an infant may be flaccid when delivered, recovery of muscle tone takes place within one or 2 minutes, and such infants have been breathing when the cord was cut.
No toxic side effects	The action at the myoneural junction appears to be remarkably specific. No other pharmacological effect is observable. The products of hydrolysis are normally occurring metabolites.

A-973 55/8/37

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

Figure 4. A 1955 advertisement in Anesthesiology

ANNIE THESIOLOGY says:

"Good gracious!
...and now WE'RE moving
JUNE THIRTIETH.

Remember, good folks,
if you write the Journal
office after that date
our address will be
3 PENN CENTER PLAZA"

now available here
the original short-acting muscle relaxant

SUXINYL®
Chloride
(brand of Succinylcholine chloride)

Useful as an adjunct to surgical anesthesia, endoscopy, manipulative procedures and electroshock therapy.

SUXINYL Chloride® is available in 10 cc. multiple-dose vials containing 20 mg. succinylcholine chloride per cc.

®Known abroad as Scoline

FOUGERA E. FOUGERA & COMPANY, INC. 75 Varick Street, New York 13, N. Y.

Figure 5. A 1957 advertisement in Anesthesia & Analgesia

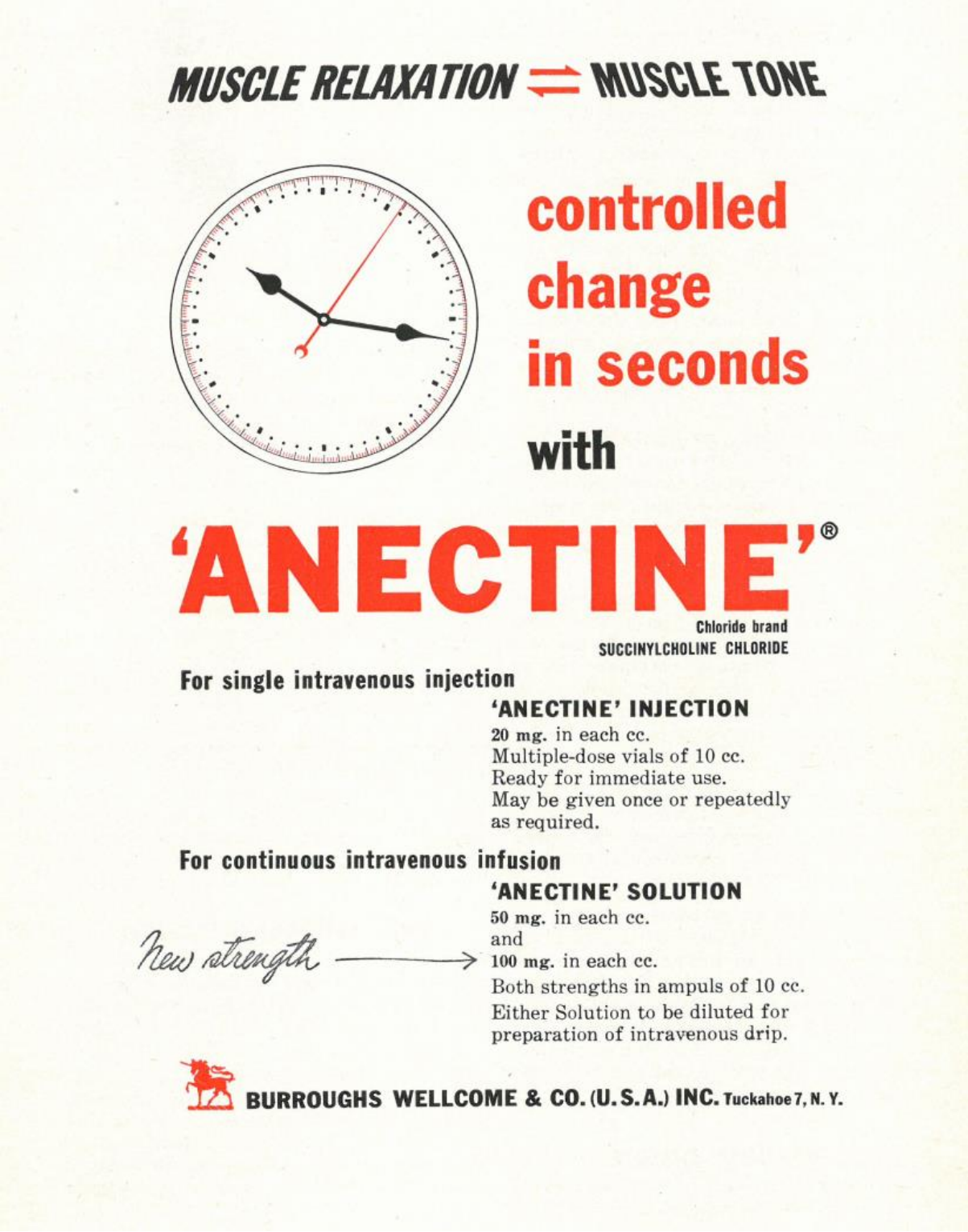


Figure 6. A 1962 BWC Anectine booklet, pages 3-6

For the Medical Profession only

'ANECTINE'®

offers these advantages

1. QUICK ACTION. The relaxing effect of 'Anectine' is apparent within 30-60 seconds after intravenous injection.

2. RAPID RECOVERY. 'Anectine' is rapidly hydrolyzed; a single intravenous injection produces relaxation of about 3 minutes duration, followed by rapid recovery.

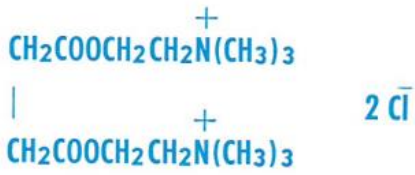
3. VIRTUALLY NO TOXICITY. The end products of 'Anectine' hydrolysis are the normally-occurring metabolites, succinic acid and choline.

4. VIRTUALLY NO SIDE EFFECTS. 'Anectine' appears to have no physiologic action except at the myoneural junction. In therapeutic dosage it does not generally influence other areas of the autonomic nervous system, blood pressure, heart rate or blood picture.

5. CONTROLLABILITY. With 'Anectine', the degree and duration of muscle relaxation is readily controlled by varying the dosage and rate of administration.

CHEMICAL PROPERTIES

Succinylcholine Chloride, also referred to as diacetylcholine chloride, is a white, odorless, crystalline substance which is readily soluble in water. Chemically it is succinic acid bis (β-dimethyl-aminoethyl) ester dimethochloride, and its formula is as follows:



The ester linkage is rapidly hydrolyzed in alkaline solutions but is relatively stable in acid solutions. In order to promote stability, solutions should be kept under refrigeration. It appears that succinylcholine is rapidly hydrolyzed following its injection and that this accounts for its extremely short duration of action and the rapid recovery of normal muscle tone.

1 Gm. 'Anectine' (the contents of one 10 cc. ampul containing 100 mg. per cc. or of one 'Flo-Pack' unit containing 1 Gm.) to 1,000 or 500 cc., respectively, of sterile 5% glucose solution or sterile isotonic saline solution. The more dilute solution (0.1% or 1 mg. per cc.) is probably preferable from the standpoint of ease of control of rate of administration of the drug and, hence, of relaxation. This intravenous drip solution containing 1 mg. per cc. may be administered at a rate of from 0.5 mg. (0.5 cc.) to 10 mg. (10 cc.) per minute to obtain the desired amount of relaxation. The amount required per minute will depend upon the individual response as well as the degree of relaxation required. In the experience of Foldes[15] the average rate is 2.5 mg. per minute. In the series reported by Little, Hampton and Grosskreutz[16] an average dose of 4.3 mg. per minute was used. The 0.2% solution may be especially useful in those cases where it is desired to avoid overburdening the circulation with a large volume of fluid, e.g. cardiac cases. In any case, the rate of administration will be varied from time to time. The degree of relaxation can be regulated to the needs of the surgeon by adjusting the drip.

NOTE: Succinylcholine is rapidly hydrolyzed by alkaline solutions and therefore loses potency rapidly if mixed with thiopental sodium (pentothal sodium). Such mixtures, if used at all, must be used within a few minutes of preparation; however, separate injection of 'Anectine' is preferable. Succinylcholine chloride is quite stable when stored under refrigeration. On standing at room temperature potency gradually decreases. The higher the concentration of a solution of Succinylcholine Chloride the more rapid will be the loss of potency at a given temperature.

CONTRAINDICATIONS AND PRECAUTIONS

Succinylcholine Chloride may produce respiratory depression as a result of general muscular paralysis. While respiratory depression is usually of very short duration following a single dose of the drug, or following cessation of continuous intravenous administration, there may on occasion be more prolonged respiratory depression requiring adequate respiratory exchange by the administration of artificial respiration. The drug should be used only by those skilled in the administration of assisted or controlled respiration and facilities for this procedure and the administration of oxygen should always be immediately available. Neostigmine and other anticholinesterases, as well as edrophonium (Tensilon) do not generally antagonize the action of Succinylcholine but, on the contrary, prolong its effect. Intravenous injection of procaine likewise may prolong the action of Succinylcholine. On rare occasions, however, Succinylcholine may produce prolonged respiratory depression due to the development

of a dual block.[8,9,26-31] Under these circumstances edrophonium may be administered in a small test dose. If improvement in spontaneous respiration occurs, additional small doses of edrophonium may result in rapid return of the spontaneous respiratory pattern.[8-11] 'Anectine' brand Succinylcholine Chloride is an ultra-short-acting skeletal muscle relaxant; that is, following intravenous injection of small doses (10 mg. to 40 mg.) the relaxation persists approximately three minutes. For prolonged relaxation 'Anectine' may be given by continuous intravenous drip. The degree of relaxation may be controlled by adjusting the rate of flow of the solution. Upon stopping the intravenous drip, spontaneous respiration ordinarily resumes within a minute and recovery is complete within 5 minutes. The quick return of spontaneous respiration is a definite advantage. Tachyphylaxis does not occur and cumulative action is not ordinarily seen.

'Anectine' should be used only by those skilled in the administration of artificial respiration. Facilities for providing adequate ventilation of the patient, including the administration of oxygen and the elimination of carbon dioxide, should always be immediately available. 'Anectine' is not an anesthetic agent and should not be regarded as a substitute for anesthesia; its use does not take the place of giving an adequate amount of anesthetic agent.

Some anesthesiologists believe that rapid injection is responsible for the muscular twitching that is seen just prior to relaxation. These fasciculations may be due to the rate of injection of the drug, and may be minimized or avoided by giving the injection more slowly.[15,32]

While respiratory depression is usually of very short duration following a single dose of the drug, or following cessation of continuous intravenous administration, there may on occasion, especially with excessive doses, be more prolonged respiratory depression[12,14] requiring artificial ventilation of the patient.

The duration of the effect of 'Anectine' may in part depend on plasma-cholinesterase activity.[33-35] Patients with severe liver disease, severe anemia, severe malnutrition, and possibly those suffering from polyphosphate insecticide poisoning may have a decreased plasma-cholinesterase activity which may intensify and prolong the action of 'Anectine', especially if large doses are used.[36,37] In such cases, in addition to the usual measures, it may be desirable to administer plasma or whole blood for the purpose of restoring cholinesterase activity.[36]

There is evidence that intraocular pressure is increased slightly following injection of 'Anectine'.[38] This effect is seen immediately after the injection and during the fasciculatory phase; it subsides as complete

paralysis supervenes; it appears to be the result of brief contraction of the extraocular muscles. This suggests that 'Anectine' should be used with caution, if at all, in intraocular surgery. The opinion is expressed that the effect is probably not sufficient to contraindicate the drug in general surgery or electroshock therapy for patients with glaucoma or in patients undergoing eye surgery under general anesthesia.[39,40]

CLINICAL OBSERVATIONS

As an aid to bronchoscopy, Reitman[17] reports that "After experience with an initial series of 100 bronchoscopies, with curare as the relaxant, it was found that succinylcholine was much better and it has been used in a second series of 100 bronchoscopies. The new technique has also been adapted for use in other surgical procedures that require excellent relaxation for short periods of time. It provides safety and comfort for the patient, permits the surgeon or bronchoscopist to do much better work, and reduces the emotional strain on all concerned."

Santos and Sweet[18] advocate the use of succinylcholine even for poor-risk patients undergoing thoracic surgery, on the basis of good results obtained with its use in 100 such patients. "Particular preference is given to succinylcholine, a depolarizing relaxant drug, because of its short duration of action, and its easy controllability of administration."

In obstetrics, the safety of succinylcholine was determined by Kvisselgaard and Moya[19] in studies of varying dosages in full-term vaginal deliveries. "... the threshold dose necessary to permit the passage of barely detectable quantities into the fetal blood is in the region of 300 mg., *i.e.* 5 to 6 times the usual clinical dose. ... None of the infants appeared to be affected by the relaxant, irrespective of the dose and time interval between injection and delivery."

In pediatric surgery, Telford and Keats[20] found that succinylcholine "allows ideal operating conditions for the surgeon even in the smallest patients, with minimal cardiac effects of anesthetic agents. ... within ten minutes from cessation of the succinylcholine drip, respiratory activity returned and by the time the operation was completed (or before) the children were moving, breathing spontaneously and adequately."

Figure 7. A 1975 BWC Anectine booklet, pages 7-9

muscles and the diaphragm. The drug has no direct effect on the myocardium. Initially a transient bradycardia accompanied by hypotension, arrhythmias and even a sinus arrest may occur during endotracheal intubation due to an increase in vagal tone. This is noted particularly in children and is more apparent with repetitive injections than following continuous intravenous drip administration. These effects are enhanced by cyclopropane and halothane and are inhibited by thiopental and atropine. Later the drug may cause tachycardia and hypertension as a result of an asphyxial pressor response and mild sympathetic ganglion stimulation.

Succinylcholine causes a slight, transient increase in intraocular pressure. The effect is seen immediately after its injection and during the fasciculation phase. It appears to be the result of brief contraction of the extraocular muscles. This suggests that the drug should not be used when open eye injury is present and should be used with caution, if at all, in intraocular surgery. The opinion is expressed that the effect is probably not sufficient to contraindicate the drug in general surgery or electroshock therapy for patients with glaucoma or in patients undergoing eye surgery under general anesthesia.

Succinylcholine has no direct effect on the uterus or other smooth muscles. The drug is highly ionized and has a low lipid solubility; therefore, it will not cross the placenta readily. Further, the enzymatic destruction of succinylcholine is an important factor in controlling the concentration gradient. Infants are relatively more resistant to depolarizing relaxants than adults.

Tachyphylaxis may occur after repeated doses of succinylcholine.

NOTE: On rare occasions when succinylcholine is given over a long period of time, the characteristic depolarization block of the myoneural junction changes to a non-depolarizing block resulting in prolonged respiratory depression or apnea similar to the blockage caused by tubocurarine. Under those circumstances small repeated doses of prostigmine may shorten the action of succinylcholine.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: Succinylcholine should be used only by those skilled in the management of artificial respiration and only when facilities are instantly available for endotracheal intubation and for providing adequate ventilation of the patient, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or to control respiration.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy: The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g. the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

DOSAGE AND ADMINISTRATION: The dosage of succinylcholine is essentially individualized and its administration should always be determined by the clinician after careful assessment of the patient.

To avoid distress to the patient, succinylcholine should be administered only after unconsciousness has been induced.

FOR SHORT SURGICAL PROCEDURES: The average dose for relaxation of short duration is 40 mg (2.0 cc) Anectine brand Succinylcholine Chloride Injection given intravenously. The optimum dose will vary among individuals and may vary from 20 to 80 mg for adults (1.0 to 4.0 cc). Following administration of doses in this range, relaxation develops in about 1 minute; maximum muscular paralysis may persist for about 2 minutes, after which recovery rapidly takes place within 8 to 10 minutes. However, very large doses may result in more prolonged apnea. An initial test dose of 10 mg (0.5 cc) may be used to determine the sensitivity of the patient and the individual recovery time from the drug.

FOR LONG SURGICAL PROCEDURES: The dosage of succinylcholine chloride administered by infusion depends upon the duration of the surgical procedure and the need for muscle relaxation. The average rate of administration for continuous intravenous infusion is 2.5 mg per minute for adult patients. Solutions containing from 0.1% to 0.2% (1 to 2 mg per cc) succinylcholine chloride have commonly been used for continuous intravenous drip. Solutions of 0.1% or 0.2% may conveniently be prepared by adding 1 g succinylcholine chloride (the contents of one Anectine brand Succinylcholine Chloride Sterile Powder Flo-Pack unit containing 1 g) respectively to 1,000 or 500 cc of sterile solution such as sterile 5% dextrose solution or sterile isotonic saline or lactate solution. The more dilute solution (0.1% or 1 mg per cc) is probably preferable from the standpoint of ease of control of the rate of administration of the drug and hence, of relaxation. This intravenous drip solution containing 1 mg per cc may be administered at a rate of from 0.5 mg (0.5 cc) to 10 mg (10 cc) per minute to

Figure 8. 1972 FDA document

NDA 13-453/S-001, S-002
NF 13-316

NOV 21 1972

Burroughs Wellcome Company
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

We acknowledge the receipt on October 16, 1972 of your communication dated October 11, 1972 regarding your supplemental new drug application of October 19, 1970 and February 2, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anectine (succinylcholine chloride) Injection.

The supplemental application provides for updating manufacturing information as required by Federal Register Notice of August 26, 1970.

We have completed our review of this supplemental application. However, before we are able to reach a final conclusion the following additional information is necessary:

Please submit information to assure the sterility of the multiple dose vials is maintained during the actual period of use of the vials. It is necessary that an analytical procedure for methylparaben be submitted to the Administration in order to confirm that the potency of the methylparaben does not decrease below the labeled quantity during the stability studies.

We have reservations concerning the stability data submitted for Anectine Injection over the 24 month storage period. We note that Anectine Injection Lot #2-P-165 is below the accepted potency of % of label amount of succinylcholine chloride after 24 months of storage at 10°C. Potency data should be reported as percent of label amount of anhydrous succinylcholine chloride.

Please submit the above information promptly.

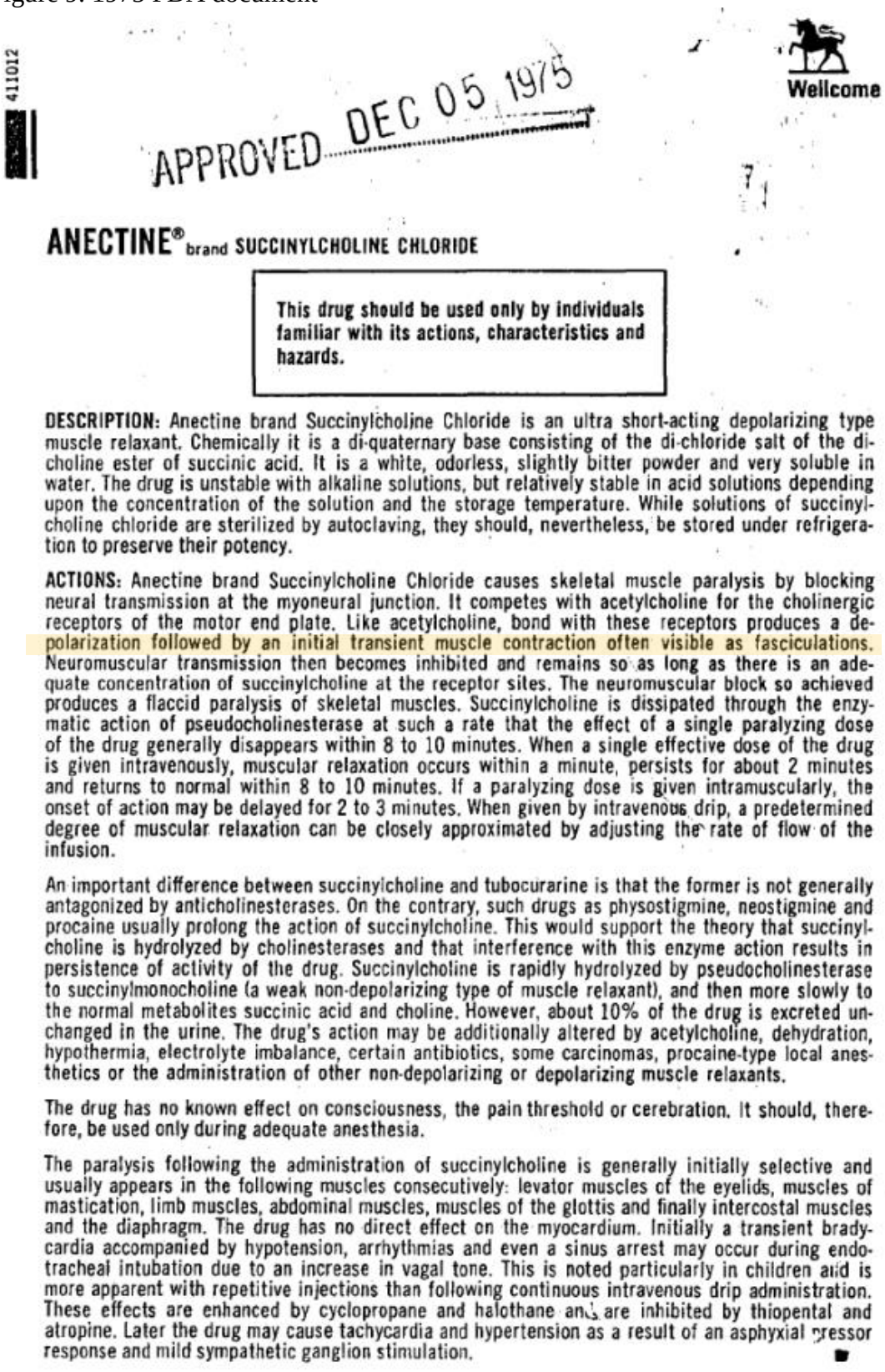
Sincerely yours,

Elmer A. Gardner, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Scientific Evaluation
Bureau of Drugs

cc: ATL-DO
OSE (BD-100)
DND (BD-120)
Med (BD-106)
IAS (BD-242)
RHBluckins/11/10/72/esr/11/16/72
R/D init. by: RShultz/11/10/72

REV/NF

Figure 9. 1975 FDA document



411012

APPROVED DEC 05 1975

Wellcome

ANECTINE® brand SUCCINYLCHOLINE CHLORIDE

This drug should be used only by individuals familiar with its actions, characteristics and hazards.

DESCRIPTION: Anectine brand Succinylcholine Chloride is an ultra short-acting depolarizing type muscle relaxant. Chemically it is a di-quaternary base consisting of the di-chloride salt of the di-choline ester of succinic acid. It is a white, odorless, slightly bitter powder and very soluble in water. The drug is unstable with alkaline solutions, but relatively stable in acid solutions depending upon the concentration of the solution and the storage temperature. While solutions of succinylcholine chloride are sterilized by autoclaving, they should, nevertheless, be stored under refrigeration to preserve their potency.

ACTIONS: Anectine brand Succinylcholine Chloride causes skeletal muscle paralysis by blocking neural transmission at the myoneural junction. It competes with acetylcholine for the cholinergic receptors of the motor end plate. Like acetylcholine, bond with these receptors produces a depolarization followed by an initial transient muscle contraction often visible as fasciculations. Neuromuscular transmission then becomes inhibited and remains so as long as there is an adequate concentration of succinylcholine at the receptor sites. The neuromuscular block so achieved produces a flaccid paralysis of skeletal muscles. Succinylcholine is dissipated through the enzymatic action of pseudocholinesterase at such a rate that the effect of a single paralyzing dose of the drug generally disappears within 8 to 10 minutes. When a single effective dose of the drug is given intravenously, muscular relaxation occurs within a minute, persists for about 2 minutes and returns to normal within 8 to 10 minutes. If a paralyzing dose is given intramuscularly, the onset of action may be delayed for 2 to 3 minutes. When given by intravenous drip, a predetermined degree of muscular relaxation can be closely approximated by adjusting the rate of flow of the infusion.

An important difference between succinylcholine and tubocurarine is that the former is not generally antagonized by anticholinesterases. On the contrary, such drugs as physostigmine, neostigmine and procaine usually prolong the action of succinylcholine. This would support the theory that succinylcholine is hydrolyzed by cholinesterases and that interference with this enzyme action results in persistence of activity of the drug. Succinylcholine is rapidly hydrolyzed by pseudocholinesterase to succinylmonocholine (a weak non-depolarizing type of muscle relaxant), and then more slowly to the normal metabolites succinic acid and choline. However, about 10% of the drug is excreted unchanged in the urine. The drug's action may be additionally altered by acetylcholine, dehydration, hypothermia, electrolyte imbalance, certain antibiotics, some carcinomas, procaine-type local anesthetics or the administration of other non-depolarizing or depolarizing muscle relaxants.

The drug has no known effect on consciousness, the pain threshold or cerebration. It should, therefore, be used only during adequate anesthesia.

The paralysis following the administration of succinylcholine is generally initially selective and usually appears in the following muscles consecutively: levator muscles of the eyelids, muscles of mastication, limb muscles, abdominal muscles, muscles of the glottis and finally intercostal muscles and the diaphragm. The drug has no direct effect on the myocardium. Initially a transient bradycardia accompanied by hypotension, arrhythmias and even a sinus arrest may occur during endotracheal intubation due to an increase in vagal tone. This is noted particularly in children and is more apparent with repetitive injections than following continuous intravenous drip administration. These effects are enhanced by cyclopropane and halothane and are inhibited by thiopental and atropine. Later the drug may cause tachycardia and hypertension as a result of an asphyxial pressor response and mild sympathetic ganglion stimulation.

Succinylcholine causes a slight, transient increase in intraocular pressure. The effect is seen immediately after its injection and during the fasciculation phase. It appears to be the result of brief contraction of the extraocular muscles. This suggests that the drug should not be used when open eye injury is present and should be used with caution, if at all, in intraocular surgery. The opinion is expressed that the effect is probably not sufficient to contraindicate the drug in general surgery or electroshock therapy for patients with glaucoma or in patients undergoing eye surgery under general anesthesia.

Succinylcholine has no direct effect on the uterus or other smooth muscles. The drug is highly ionized and has a low lipid solubility; therefore, it will not cross the placenta readily. Further, the enzymatic destruction of succinylcholine is an important factor in controlling the concentration gradient. Infants are relatively more resistant to depolarizing relaxants than adults.

Tachyphylaxis may occur after repeated doses of succinylcholine.

NOTE: On rare occasions when succinylcholine is given over a long period of time, the characteristic depolarization block of the myoneural junction changes to a non-depolarizing block resulting in prolonged respiratory depression or apnea similar to the blockade caused by tubocurarine. Under those circumstances small repeated doses of prostigmine may shorten the action of succinylcholine.

INDICATIONS: Succinylcholine chloride is indicated as an adjunct to anesthesia to induce skeletal muscle relaxation. It may be employed to reduce the intensity of muscle contractions of pharmacologically or electrically induced convulsions.

CONTRAINDICATIONS: Succinylcholine is contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: Succinylcholine should be used only by those skilled in the management of artificial respiration and only when facilities are instantly available for endotracheal intubation and for providing adequate ventilation of the patient, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or to control respiration.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe, or administered simultaneously during intravenous infusion through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in Pregnancy: The safe use of succinylcholine has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels of, or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following the use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered with extreme care to such patients and dosage should be minimal. If low plasma cholinesterase activity is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered, or relaxation may be produced by the cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase, such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently with succinylcholine.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Great caution should be observed also in patients with

pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury, or have degenerative or dystrophic neuromuscular disease, as such patients tend to become severely hyperkalemic when succinylcholine is given.

When succinylcholine is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction may change to a non-depolarizing block which results in prolonged respiratory depression or apnea. Under such circumstances, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator (e.g. the Wellcome Peripheral Nerve Stimulator) may be used to ascertain the type of neuromuscular blockade. If a depolarization block is present both fast (tetanic) and slow (twitch) rates of nerve stimulation are well sustained, and post-tetanic facilitation is absent. If a non-depolarizing block is present there is post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation.

Succinylchloride should be used with caution during ocular surgery and in patients with glaucoma. The drug should be employed with caution in patients with fractures or muscle spasm as the muscle fasciculations may cause additional trauma. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a non-depolarizing relaxant. If other relaxants are to be used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

During the past few years, reports have called attention to a fulminant syndrome, malignant hyperthermia, observed during anesthesia. Its etiology is not fully understood. Malignant hyperthermia occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of the concomitant use of a muscle relaxant, but may be triggered by succinylcholine. Because of the seriousness of this syndrome and the need for early effective treatment of the patient, it is suggested that the continuous monitoring of the temperature will serve as an aid to the early recognition of malignant hyperthermia.

ADVERSE REACTIONS: Adverse reactions consist primarily of an extension of the drug's pharmacological actions. Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances.

The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

DOSAGE AND ADMINISTRATION: The dosage of succinylcholine is essentially individualized and its administration should always be determined by the clinician after careful assessment of the patient.

To avoid distress to the patient, succinylcholine should be administered only after unconsciousness has been induced.

FOR SHORT SURGICAL PROCEDURES: The average dose for relaxation of short duration is 40 mg (2.0 cc) Anectine brand Succinylcholine Chloride Injection given intravenously. The optimum dose will vary among individuals and may vary from 20 to 30 mg for adults (1.0 to 4.0 cc). Following administration of doses in this range, relaxation develops in about 1 minute; maximum muscular paralysis may persist for about 2 minutes, after which recovery rapidly takes place within 8 to 10 minutes. However, very large doses may result in more prolonged apnea. An initial test dose of 10 mg (0.5 cc) may be used to determine the sensitivity of the patient and the individual recovery time from the drug.

FOR LONG SURGICAL PROCEDURES: The dosage of succinylcholine chloride administered by infusion depends upon the duration of the surgical procedure and the need for muscle relaxation. The average rate of administration for continuous intravenous infusion is 2.5 mg per minute for adult patients. Solutions containing from 0.1% to 0.2% (1 to 2 mg per cc) succinylcholine chloride have commonly been used for continuous intravenous drip. Solutions of 0.1% or 0.2% may conveniently be prepared by adding 1 g succinylcholine chloride (the contents of one 10 cc ampul containing 100 mg per cc or of one Anectine brand Succinylcholine Chloride Sterile Powder Flo-Pack unit containing 1 g) respectively to 1,000 or 500 cc of sterile solution such as sterile 5% dextrose solution or sterile isotonic saline or lactate solution. The more dilute solution (0.1% or 1 mg per cc) is probably preferable from the standpoint of ease of control of the rate of administration of the drug and hence, of relaxation. This intravenous drip solution containing 1 mg per cc may be administered at

Table 1. The year of appearance of select adverse effects of succinylcholine in journals, textbooks in anesthesiology, and drug package inserts.

Adverse reaction	Year when adverse reaction appeared in literature	Year when adverse reaction appeared in different textbooks	Year when advers com
Bradycardia	*1952 – Thesleff S. The pharmacological properties of succinylcholine iodide; with particular reference to its clinical use as a muscular relaxant. Acta Physiol Scand. 1952;26:103-29. 1957 – Leigh MD, McCoy DD, Belton MK, Lewis GB. Bradycardia following intravenous administration of succinylcholine chloride to infants and children. Anesthesiology. 1957;18:698-702. 1958 – Martin KH. International Symposium on Curare and Curare-like Drugs. Atti XI Congresso Societa Italiana de Anestesiologia, Venezia. September 1958, p. 362. 1959 – Bullough J. Intermittent Suxamethonium Injections. Br Med J. 1959;1:786-787.	1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960. 1965 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 3rd ed. New York: The Macmillan Company; 1965. 1966 – Collins VJ. Principles of Anesthesiology. Philadelphia: Lea & Febiger; 1966. 1967 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 3rd ed. Philadelphia: WB Saunders Company; 1967.	1975 – Burroughs W “Anectine” booklet Reactions” sections 1975 – Burroughs W “Anectine” FDA do
Fasciculations	1952 – Thesleff S. The pharmacological properties of succinylcholine iodide; with particular reference to its clinical use as a muscular relaxant. Acta Physiol Scand. 1952;26:103-29. 1952 – Butt NS. A report on the use of succinylcholine chloride in a thoracic unit. Br J Anaesth. 1952;24:245-51. 1952 – Foldes FF, McNall PG, Borrego-Hinojosa JM. Succinylcholine: a new approach to muscular relaxation in anesthesiology. N Engl J Med. 1952;247:596-600.	1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960. 1961 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 2nd ed. Philadelphia: WB Saunders Company; 1961. 1965 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 3rd ed. New York: The Macmillan Company; 1965. 1966 – Collins VJ. Principles of Anesthesiology. Philadelphia: Lea & Febiger; 1966.	1952 (estimated) – Company “Anectin and Precautions” se 1954 (estimated) – Company “Anectin section. 1962 – Burroughs W “Anectine” booklet Precautions” sectio
Myalgia	1952 – Bourne JG, Collier HO, Somers GF. Succinylcholine (succinoylcholine) muscle-relaxant of short action. Lancet. 1952;259(6721):1225-9. 1954 – Churchill-Davidson HC. Suxamethonium (succinylcholine) chloride	1955 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 2nd ed. New York: The Macmillan Company; 1955. 1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-	1975 – Burroughs W “Anectine” booklet Reactions” sections 1975 – Burroughs W “Anectine” FDA do

	and muscle pains. Br Med J. 1954;1(4853):74. 1956 – Hegarty P. Postoperative muscle pains. Br J Anaesth. 1956;28(5):209-12.	Luke; 1960. 1961 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 2nd ed. Philadelphia: WB Saunders Company; 1961.	
Prolonged apnea	1952 – Bourne JG, Collier HO, Somers GF. Succinylcholine (succinoylcholine), muscle-relaxant of short action. Lancet. 1952;1:1225-9. 1952 – Evans FT, Gray PW, Lehmann H, Silk E. Sensitivity to succinylcholine in relation to serum-cholinesterase. Lancet. 1952;259(6721):1229-30. 1953 – Bourne, JG. Long action of suxamethonium (succinylcholine) chloride. Br J Anaesth. 1953;25:116-29. 1953 – Forbat A, Lehmann H, Silk E. Prolonged apnoea following injection of succinyldicholine. Lancet. 1953;262(6795):1066-8.	1955 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 2nd ed. New York: The Macmillan Company; 1955. 1957 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 1st ed. Philadelphia: WB Saunders Company; 1957. 1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960. 1961 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 2nd ed. Philadelphia: WB Saunders Company; 1961.	1952 (estimated) – Company "Anectin and Precautions" se 1962 – Burroughs W "Anectine" booklet Precautions" sectio
Hyperkalemia	1960 – Stevenson D. Changes in the blood electrolytes of anaesthetized dogs caused by suxamethonium. Br J Anaesth. 1960;32:364-71. 1962 – Bush GH, Graham HA, Littlewood AH, Scott LB. Danger of suxamethonium and endotracheal intubation in anaesthesia for burns. Br Med J. 1962;2:1081-5. 1963 – McCaughey TJ. Burn Mortality and the Anaesthetist. Can Anaesth Soc J. 1963;10:501-7. 1969 – Schaner PJ, Brown RL, Kirksey TD, Gunther RC, Ritchey CR, Gronert GA. Succinylcholineinduced hyperkalemia in burned patients. 1. Anesth Analg. 1969;48:764-70	1965 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 3rd ed. New York: The Macmillan Company; 1965. 1967 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 3rd ed. Philadelphia: WB Saunders Company; 1967. 1976 – Collins VJ. Principles of Anesthesiology. 2nd ed. Philadelphia: Lea & Febiger; 1976.	1975 – Burroughs W "Anectine" booklet 1975 – Burroughs W "Anectine" FDA do
Malignant hyperthermia	1966 – Thut WH, Davenport HT. Hyperpyrexia associated with succinylcholine-induced muscle rigidity: a case report. Can Anaesth Soc J. 1966;13:425-8	1970 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 4th ed. New York: The Macmillan Company; 1970. 1976 – Collins VJ. Principles of	1975 – Burroughs W "Anectine" booklet 1975 – Burroughs W "Anectine" FDA do

	1969 – Murray BR, Williams PA. Malignant hyperpyrexia during anaesthesia for colectomy. Br Med J. 1969;1:488 1980 – Denborough MA. The pathopharmacology of malignant hyperpyrexia. Pharmacol Ther. 1980;9:357-65	Anesthesiology. 2nd ed. Philadelphia: Lea & Febiger; 1976.	

*In doses >30mg/kg (animal studies)

Table 1. The year of appearance of select adverse effects of succinylcholine in journals, textbooks in anesthesiology, and drug package inserts.

Adverse reaction	Year when adverse reaction appeared in literature	Year when adverse reaction appeared in different textbooks	Year when advers com
Bradycardia	*1952 – Thesleff S. The pharmacological properties of succinylcholine iodide; with particular reference to its clinical use as a muscular relaxant. Acta Physiol Scand. 1952;26:103-29. 1957 – Leigh MD, McCoy DD, Belton MK, Lewis GB. Bradycardia following intravenous administration of succinylcholine chloride to infants and children. Anesthesiology. 1957;18:698-702. 1958 – Martin KH. International Symposium on Curare and Curare-like Drugs. Atti XI Congresso Societa Italiana de Anestesiologia, Venezia. September 1958, p. 362. 1959 – Bullough J. Intermittent Suxamethonium Injections. Br Med J. 1959;1:786-787.	1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960. 1965 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 3rd ed. New York: The Macmillan Company; 1965. 1966 – Collins VJ. Principles of Anesthesiology. Philadelphia: Lea & Febiger; 1966. 1967 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 3rd ed. Philadelphia: WB Saunders Company; 1967.	1975 – Burroughs W "Anectine" booklet Reactions" sections 1975 – Burroughs W "Anectine" FDA do
Fasciculations	1952 – Thesleff S. The pharmacological properties of succinylcholine iodide; with particular reference to its clinical use as a muscular relaxant. Acta Physiol Scand. 1952;26:103-29. 1952 – Butt NS. A report on the use of succinylcholine chloride in a thoracic unit. Br J Anaesth. 1952;24:245-51. 1952 – Foldes FF, McNall PG, Borrego-Hinojosa JM. Succinylcholine: a new approach to muscular relaxation in anesthesiology. N Engl J Med. 1952;247:596-600.	1955 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 2nd ed. New York: The Macmillan Company; 1955. 1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960. 1961 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 2nd ed. Philadelphia: WB Saunders Company; 1961.	1952 (estimated) – Company "Anectin and Precautions" se 1954 (estimated) – Company "Anectin section. 1962 – Burroughs W "Anectine" booklet Precautions" sectio
Myalgia	1952 – Bourne JG, Collier HO, Somers GF. Succinylcholine (succinoylcholine) muscle-relaxant of short action. Lancet. 1952;259(6721):1225-9. 1954 – Churchill-Davidson HC. Suxamethonium (succinylcholine) chloride and muscle pains. Br Med J.	1955 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 2nd ed. New York: The Macmillan Company; 1955. 1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960.	1975 – Burroughs W "Anectine" booklet Reactions" sections 1975 – Burroughs W "Anectine" FDA do

	1954;1(4853):74. 1956 – Hegarty P. Postoperative muscle pains. Br J Anaesth. 1956;28(5):209-12.	 1961 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 2nd ed. Philadelphia: WB Saunders Company; 1961.	
Prolonged apnea	1952 – Bourne JG, Collier HO, Somers GF. Succinylcholine (succinoylcholine), muscle-relaxant of short action. Lancet. 1952;1:1225-9. 1952 – Evans FT, Gray PW, Lehmann H, Silk E. Sensitivity to succinylcholine in relation to serum-cholinesterase. Lancet. 1952;259(6721):1229-30. 1953 – Bourne, JG. Long action of suxamethonium (succinylcholine) chloride. Br J Anaesth. 1953;25:116-29. 1953 – Forbat A, Lehmann H, Silk E. Prolonged apnoea following injection of succinyldicholine. Lancet. 1953;262(6795):1066-8.	1955 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 2nd ed. New York: The Macmillan Company; 1955. 1957 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 1st ed. Philadelphia: WB Saunders Company; 1957. 1960 – Wylie WD, Davidson HCC. A Practice of Anaesthesia. London: Lloyd-Luke; 1960.	1952 (estimated) – Company "Anectin and Precautions" se 1962 – Burroughs W "Anectine" booklet Precautions" sectio
Hyperkalemia	1960 – Stevenson D. Changes in the blood electrolytes of anaesthetized dogs caused by suxamethonium. Br J Anaesth. 1960;32:364-71. 1962 – Bush GH, Graham HA, Littlewood AH, Scott LB. Danger of suxamethonium and endotracheal intubation in anaesthesia for burns. Br Med J. 1962;2:1081-5. 1963 – McCaughey TJ. Burn Mortality and the Anaesthetist. Can Anaesth Soc J. 1963;10:501-7. 1969 – Schaner PJ, Brown RL, Kirksey TD, Gunther RC, Ritchey CR, Gronert GA. Succinylcholineinduced hyperkalemia in burned patients. 1. Anesth Analg. 1969;48:764-70	1965 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 3rd ed. New York: The Macmillan Company; 1965. 1967 – Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia. 3rd ed. Philadelphia: WB Saunders Company; 1967. 1976 – Collins VJ. Principles of Anesthesiology. 2nd ed. Philadelphia: Lea & Febiger; 1976.	1975 – Burroughs W "Anectine" booklet 1975 – Burroughs W "Anectine" FDA do
Malignant hyperthermia	1966 – Thut WH, Davenport HT. Hyperpyrexia associated with succinylcholine-induced muscle rigidity: a case report. Can Anaesth Soc J. 1966;13:425-8	1970 – Goodman LS, Gillman A. The Pharmacological Basis of Therapeutics. 4th ed. New York: The Macmillan Company; 1970. 1976 – Collins VJ. Principles of	1975 – Burroughs W "Anectine" booklet 1975 – Burroughs W "Anectine" FDA do

	1969 – Murray BR, Williams PA. Malignant hyperpyrexia during anaesthesia for colectomy. Br Med J. 1969;1:488 1980 – Denborough MA. The pathopharmacology of malignant hyperpyrexia. Pharmacol Ther. 1980;9:357-65	Anesthesiology. 2nd ed. Philadelphia: Lea & Febiger; 1976.	

*In doses >30mg/kg (animal studies)

Succinylcholine, a depolarizing neuromuscular blocker, was introduced into clinical practice in 1953.

It was associated with hyperkalemia and malignant hyperthermia.

These potential side effects were not known to the manufacturer when the drug was introduced.

We found no evidence that Burroughs Wellcome and Company, New York [the manufacturer] suppressed information about these side effects.

After several decades of clinical use, succinylcholine continues to be used throughout the world, although newer neuromuscular blockers and reversal agents may affect its popularity.